David Ross Chason
Licensed Pharmacist, Consultant

Box Hill Surgery Center
And
Office Practice of Ritu T. Bhambhani, MD

Address:

Box Hill Surgery Center
100 Walter Ward Blvd.
Abingdon, Md. 21009

Reviewer:

David Ross Chason, RPh, MBA
Maryland Pharmacist License Number 07477
License Expiration 3/31/2017
Curriculum Vitae – attached

I. Documents reviewed:

A. Medical Records for eight (8) patients.
Review of medical record documents, completed Directives for Resuscitation forms, informed consent forms, pre-procedure assessments, post-procedure assessments, treatment safety check forms, PACU forms, postsurgical standard order forms, and advanced directives for eight (8) patients.

B. Transcripts of the depositions of Ritu T. Bhambhani, MD, Andrew Vickers, RN and YuZon Wu.

C. Exhibits relating to Box Hill Surgery Center policies and procedures.

D. NECC Advertisement Marked GSP DP 8, produced in response to a request for production of documents by Greenspring Surgery Center, LLC in *Helena Trope, et al. v. Greenspring Surgery Center, LLC, et al.*, HCA No. 2014-297(Maryland Health Care Alternative Dispute Resolution Office).

II. Conclusions:

My review of depositions and related documents was conducted from the perspective of a pharmacist with experience in the development and management of sterile compounding operations in hospitals and of a free standing compounding pharmacy while serving as a pharmacist, hospital pharmacy director and administrator. I have additional experience in the development and administration of regulations and training of state inspectors for sterile compounding resulting from eight (8) years serving as a commissioner of the Maryland Board of Pharmacy.

Based on this perspective, there are five (5) deficiencies noted in Dr. Bhambhani's clinical practice as well as seven (7) issues noted in the practices of the Box Hill Surgery Center.

It is clear that operational failures at New England Compounding Center (NECC) were the cause of the methylprednisolone acetate (MPA) contamination involved in the 2012 fungal infection outbreak and that NECC's practices facilitated the appearance that it was closely regulated and operated as safely as a manufacturer. The lack of knowledge about compounding practices and failure to adhere to good operational and clinical practice relating to pharmaceuticals by Dr. Bhambhani and her staff, however, provides the basis to conclude that had Dr. Bhambhani known and followed laws and regulations regarding the rules for writing prescriptions, understood the differences between compounding and manufacturing, done the appropriate amount of due diligence on the choice of vendors, and followed appropriate procedures for handling, storage and use of vials of preservative free MPA, her patients would not have been placed at risk of serious infection in 2012.

A. Background:

There are several issues involving the availability and use of pharmaceuticals over time that impacted the events in this case leading to the death and disability of patients caused by the administration of injectable medication, compounded by NECC, at Box Hill Surgery Center in Maryland. Upjohn Laboratories received Food and Drug Administration (FDA) approval to market Depo-Medrol ® in 1982. Depo-Medrol® is the brand name for MPA. It is important to note that based on the solubility and approved uses of the drug, all manufactured versions of brand name Depo-Medrol® product contained a preservative. The patent on Depo-Medrol® and many other commonly used brand name drug products began to expire in the late 1990's. The patent expiration issue resulted in significant changes in the pharmaceutical market. The entry of generic manufacturers and reductions in reimbursement ushered in a period of significant pharmaceutical shortages. According to the Department of Health and Human Services (HHS), shortages of some commonly used injectable drugs began in 2000 and continue to be an issue.

As shortages of some of these pharmaceuticals worsened, the cost of products that returned to the market increased dramatically. In some situations only one form or size of a product was available which increased waste or required increased manipulation of the product. The development and differentiation of specialized compounding pharmacies in the medical marketplace occurred as a result of these shortages and resulting need to find ways to manipulate the available manufactured products. Hospital pharmacists in response began preparing small quantities of these unavailable products as part of their provision of sterile injectable preparations used for treatment of hospitalized patients. The availability of equipment, technology and training in these hospital sites facilitated transfer of the knowledge of compounding functions into for-profit retail or specialty pharmacies that previously had concentrated on non-sterile compounding of custom pharmaceuticals based on specific physician orders.

The U.S. Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food

ingredients, and dietary supplements manufactured, distributed and consumed worldwide. USP first published a new sterile compounding standard, USP 797, in 2004. This set of standards established the basis for quality sterile compounding by providing guidance for safe handling of pharmaceuticals intended for use in the United States. These standards were developed to be enforceable and became the basis for development of laws and regulations implemented by state boards of pharmacy to provide oversight to pharmacies across the country. The new pharmacy regulations provided the basis for enforcement of rules for sterile compounding at the state level but many states implemented the standards slowly and inconsistently. There were significant delays and limitations in implementation due to lack of training and expertise in the inspection and enforcement process at the board level. Notably, USP 797 standards were not intended to apply to the pharmaceutical manufacturing industry because the manufacture of sterile products, under more restrictive standards, was already under the direct control of the FDA.

Throughout the 2000s there has been significant and ongoing conflict between the compounding pharmacy industry, state boards of pharmacy and the FDA regarding the authority to provide oversight in this high risk area of patient care. The compounding industry successfully lobbied Congress which resulted in state boards of pharmacy retaining oversight if the compounding entity operated in a manner in which there was a direct physician to patient to pharmacist relationship. This triad relationship was (and is) demonstrated by the physician generating a prescription for a specific drug, for a specific patient that was to be prepared by the pharmacy as a result of receipt of the prescription or prepared in anticipation of a known volume of orders. Regardless of the timing of preparation, a patient specific prescription for the medication is a requisite.

B. FDA Issues:

The FDA imposes stringent requirements on a company that seeks to qualify as a manufacturer of pharmaceuticals. This process involves requiring that the company register with the FDA, and perform animal and human research, using standardized procedures. The research is intended to validate the effectiveness, safety, purity, and stability of each product. Manufacturers of generic products are not required to perform all of the research functions if the product can be demonstrated to be essentially the same as the existing branded product. In all cases FDA registered manufacturers must adhere to rigorous good manufacturing processes to assure the safety and efficacy of their products and the FDA conducts inspections on their compliance,

Compounding involves the manipulation of sterile or non-sterile pharmaceutical components based on the prescription of a physician. The compounding process is intended to result in a stable, sterile prescription product. There is no standardized evaluation of the effectiveness of the final compounded product. The responsibility of the physician therefore is to determine the therapeutic efficacy of the compounded product. The compounding pharmacy is responsible for assuring that the appropriate components are in the mixture and that the final product is sterile and retains the labeled potency until the beyond use date (BUD). This separation of responsibility for all of the processes has resulted in the loss of much of the safety and control that is needed.

III. Practice Issues of Ritu T. Bhambhani, MD

A. Prescription writing

Dr. Bhambhani trained and has practiced as a hospital anesthiologist. See Bhambhani Deposition, 2/10/16, Exhibit 1054 (CV of Ritu T. Bhambhani, M.D.). An anesthiologist typically has significant experience and expertise in the pharmacology of and dosage forms of a very limited number of medications and does not write very many prescriptions for patients. This experience results in a deep knowledge of a limited number of medications. Anesthesiologists in the hospital or surgery setting often use order forms or rely on other staff to obtain pharmaceuticals. This, of course, does not relieve Dr. Bhambhani or other doctors of their responsibilities relating to prescribing and administration of prescription drugs, and when responsible for their source, as here, the source of the drugs as well.

Dr. Bhambhani later began a practice in pain management which again provided for use of a limited number of targeted pharmaceuticals. This lack of experience likely resulted in a knowledge deficit regarding the requirements for establishing a direct physician, patient, pharmacist relationship for prescription writing. The fact that many of the pharmaceuticals used were being ordered for administration in the office by the physician facilitated this breakdown in process. It should also be noted that it was to the advantage of the compounding pharmacy to break the patient specific ordering relationship so that they could bypass the requirements that would by imposed by the FDA. (References: Bhambhani Deposition, T. 110, l. 20-25; T. 111, 112; T. 113, l. 1-5; T. 120, l. 8-14).

B. Compliance with regulations

Dr. Bhambhani did not understand the need to review Maryland regulations. She did not perform any documented research regarding appropriate prescription writing practices as listed in Maryland Health General Regulations. This failure was confirmed in the deposition. (Bhambhani Deposition, 2/10/16, T. 87, l. 3-19; T. 103, l.11-20;T. 116, l. 12-25; T. 117, l. 1-5).

C. Use of inappropriate nomenclature

Dr. Bhambhani demonstrated a lack of understanding of appropriate nomenclature for pharmaceuticals. Each patient record indicated that Depo Medrol in a preservative free form was administered to the patient. The brand name form of "Depo Medrol" however, has never existed in a preservative free form which indicates a lack of knowledge appropriate of product naming, which according to the Institute for Safe Medication Practices (ISMP) is a significant risk for medication error. It would have been correct procedure to preprint the forms with the actual name of the pharmaceutical, methylprednisolone acetate. (Bhambhani Deposition, 2/10/16, T. 109, l. 5-15).

D. Research on compounded products

Dr. Bhambhani did not perform any research to confirm the safety or efficacy of the pharmaceuticals that she was injecting in high risk, non-FDA approved (i.e.- indicated) procedures. The extent of the decision to use NECC product was based on previous use without performing any research on whether the provider was licensed to

manufacture or compound the product. Additionally, Dr. Bhambhani did not research the impact of compounding versus manufacturing on the particle size of the resulting products in spite of the knowledge she described in the risks associated with injection of products with larger particle sizes. (Bhambhani Deposition, 2/10/16, Exhibit 1051 (Exhibit 1, Answers to PSC's First Set of Interrogatories, Answers to No. 1 and 7); T. 108, l. 17-25; T. 109, l. 1-4; T. 173, l. 21-25; T. 174; T. 175, l. 1-3; T. 179, l. 23-25; T. 180, l. 1-13).

E. Personal research practices

Dr. Bhambhani demonstrated that she did not perform adequate research when she referred to the Physician's Desk Reference (PDR) as the source for any research or education practices. This reference is recognized throughout the medical community as a compilation of manufacturer provided package inserts only, which should never be used solely as an authoritative reference. In addition, there are no generic products listed and therefore information would only be applicable to the branded product described in the PDR. (Bhambhani Deposition, 2/10/16, T. 77, l. 12-25; T. 78, l. 1-2; T.80, l. 10-16).

IV. Box Hill Surgery Center Facility Issues:

A. Development of Surgery Center policy and procedure

The template for this surgery center's policy and procedures was provided by a business management vendor. Although a template was a good starting point, the development and management of the policies should have been refined and customized to meet the needs of the particular organization. Going beyond this, Box Hill's pharmaceutical policies that existed were not followed. This is noted specifically in reference to the storage of the drug in the preparation area, the inappropriate use of what are in effect single dose vials (see my further discussion below on Box Hill's use of 5mL vials of MPA-PF), and the disregard for the recommendations in the policy manual "FAQ on Single Dose/Single Use Vials." Box Hill's infection control procedures contained references to entities that do not exist in a single practice surgery center. It should be noted that there is also reference in the procedure documentation indicating that "medical director will serve as the pharmaceutical services supervisor." This title does not have further explanation of the role and there is no similar title in Maryland Pharmacy Law or Regulation. The services provided in a surgery center do not come under the purview of Maryland Board of Pharmacy. Any reference to pharmaceutical services would require a pharmacy license and the services of a Maryland licensed pharmacist. (Bhambhani Deposition, 2/10/16, T. 58, l. 12-24; and Bates Numbered Box Hill Surgery Center (BHSC) Policy and Procedure Manual pages effective in 2012: BHSC0658, BHSC1006, BHSC1007, BHSC1012, and BHSC1014).

B. Vendor review process

All hospitals and related organizations such as an ambulatory surgery center develop a process for documentation of an initial and ongoing vendor review process to assure the continuous availability and quality of all of the products that are in use in the institution. In undertaking to operate and manage an ambulatory surgical procedure center as well

as a result of her previous background in hospitals and surgery centers, Dr. Bhambhani should have been aware that all vendors must be monitored through ongoing checks of licensure, quality assurance and business practice. (Bhambhani Deposition, 2/10/16, T. 87-103,187).

C. Storage and refrigeration practices

As described by Dr. Bhambhani and Mr. Vickers, the procedure at Box Hill was to store the compounded pharmaceuticals in the surgery area of the center. The recommended practice is not to store vials in the operating suite. There was no documentation that the vendor conducted research to determine whether the compounded products required storage under refrigeration. Appropriate storage and handling of compounded products are critical to minimize any growth of organisms. The information provided in the documents indicates that the vendor recommended that the products be stored under room conditions. It is likely that the storage of the preservative free methylprednisolone acetate under room temperature conditions instead of under refrigeration contributed to an increased growth of the organisms that resulted in patient infections. (Bhambhani Deposition, 2/10/16, T. 151, l. 24-25; T. 152, l. 1-20; Vickers Deposition, 2/18/16, T. 61, l. 15-25; T. 62, l. 1-12; NECC Advertisement from GSP DP 8).

D. Errors in documentation of product use

Review of the intraoperative records indicates that on occasion errors in documentation of the dose of medication occurred. The preprinted portion of the form indicated Depo Medrol 80mg with a blank space to insert the volume of the product in milliliters (mL) that was injected. In multiple instances the number that was hand written in was "40," most likely indicating that 40 mg was instilled. This type of error, although it seems minor in a single physician practice situation, provides another indication that record-keeping was not given the priority that a medical record requires. (Reference: Farthing medical record page 29).

E. Tracking of patient specific drug lot numbers and expiration dates (BUD)

The single most critical deficiency that is apparent in the documentation provided is there was a failure to track and record the lot number and expiration date of each vial of methylprednisolone acetate on the patient intraoperative data form. It is documented that the vials purchased from NECC, with a specific patient name, were actually clearly intended by the compounding pharmacy and Dr. Bhambhani to be used on another patient. This in itself is a prescribing practice violation, but if the physician or nurse would have noted on the record a lot number and expiration of the specific vial used in a procedure, there would have been direct traceability back to the specific patient when the recall was issued. This tracking would have allowed a more rapidly generated and complete list of patients who could be notified and told to seek immediate assessment.

F. Deficiencies in handling of single dose vials

The responsibility for the initial fungal contamination of the methylprednisolone acetate during the compounding process has been traced to NECC. The aseptic handling practices for essentially single dose vials by Dr. Bhambhani likely may also be a contributing factor in increasing patient risk. Injectable products that are sold without a preservative are intended for one time use. The appropriate process requires that the

operator clean the entry port of the vial with sterile alcohol and using a sterile, single use, needle and syringe enter the vial to withdraw the exact dose of the medication. There is no appropriate or approved practice that allows the vial to be used again for a second or third withdrawal regardless of the situation. The fact that the Surgery Center ordered 5 mL vials for patient treatments that required one (1) to two (2) mL of methylprednisolone acetate, especially when the vial was purchased and labeled as preservative free, indicates a significant lack of knowledge on the part of the physician and nurse.

A. Deficiencies in Root Cause Analysis process

The process for conducting a root cause analysis must be understood by health care professionals before the point when an incident occurs. The steps required and the goals to be achieved are critical to a successful outcome. Upon learning of the death of one patient and the serious condition of another patient, Dr. Bhambhani and Mr. Vickers conducted a root cause analysis that was focused on their specific office practices only and as a result did not conduct a thorough enough review of the possible causes of what turned out to be a serious outbreak of fungal infections. This is confirmed by the decision to sequester the recalled NECC MPA product they had on hand while borrowing additional product obtained from the same source (NECC) from another surgery center. A more thorough analysis would have reduced the risk to patients from use of other contaminated products and given Dr. Bhambhani additional information to share with investigators. (Sentinel Event Analysis (BHSC 000922-000925)

Expert Qualifications: See attached *Curriculum Vitae.*

Trials & depositions: During the previous four years, I have not given expert testimony in any trials or depositions.

Compensation: My hourly fee for research, consultations, reports, and testimony by deposition or at trial is $250.00 per hour.

I reserve the right to modify or supplement my opinions after further research, review of additional documents, articles, depositions, or any other material as discovery is ongoing in these cases.

David Ross Chason

Date: September 13, 2016